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THE ESTIMATED COST FOR THIS REQUEST IS 22.56 U.S. DOLLARS

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L11 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:719484 CAPLUS

DOCUMENT NUMBER: 139:247494

TITLE: Method and system for separation and
purification of narcotic alkaloids using
reversed-phase preparative
chromatography

INVENTOR(S): Antonini, Enrico A.

PATENT ASSIGNEE(S): Mallinckrodt Inc., USA

SOURCE: PCT Int. Appl., 73 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2003074526 | A2 | 20030912 | WO 2003-US4498 | 20030218 |
| WO 2003074526 | A3 | 20031204 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| CA 2477739 | A1 | 20030912 | CA 2003-2477739 | 20030218 |
| AU 2003216279 | A1 | 20030916 | AU 2003-216279 | 20030218 |
| EP 1487838 | A2 | 20041222 | EP 2003-743676 | 20030218 |
| EP 1487838 | B1 | 20080903 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | |
| CN 1639166 | A | 20050713 | CN 2003-804869 | 20030218 |
| JP 2005522460 | T | 20050728 | JP 2003-572994 | 20030218 |
| AT 407136 | T | 20080915 | AT 2003-743676 | 20030218 |
| ES 2312798 | T3 | 20090301 | ES 2003-743676 | 20030218 |
| US 20050182257 | A1 | 20050818 | US 2004-501353 | 20040714 |
| MX 2004008213 | A | 20050516 | MX 2004-8213 | 20040824 |
| IN 2004CN01890 | A | 20070720 | IN 2004-CN1890 | 20040825 |
| ZA 2004005932 | A | 20060531 | ZA 2004-5932 | 20060316 |
| PRIORITY APPLN. INFO.: | | | US 2002-360321P | P 20020228 |
| | | | US 2002-434597P | P 20021216 |
| | | | WO 2003-US4498 | W 20030218 |

AB Narcotic alkaloids are separated by feeding a crude alkaloids solution into a chromatog. column containing a compressed reversed-phase stationary phase, applying an acidic solution (pH 2-5) to the chromatog. column to recover eluates containing morphine, codeine, oripavine, papaverine, thebaine, and narcotine, resp. from the chromatog. column, adding a caustic solution to resp. eluate to precipitate and sep. the alkaloid. The mobile phase can be acetonitrile, water, ethanol, and iso-propanol. The stationary phase can consist of chemical modified silica, titania, zirconia, or a polymer. The acidic solution can contain acetic acid, formic acid, oxalic acid, succinic

acid, lactic acid, and tartaric acid. A reagent can be added to the crude alkaloid solution, such as triethylamine, tetrabutylammonium hydrogen sulfate, sodium dodecyl sulfate, sodium heptane sulfonate, or ammonium sulfate. The caustic solution can contain NaOH, KOH, NH₄OH, and carbonate salts of alkali metals. A system for separating at least one narcotic alkaloid consists of a chromatog. column having a fluid chamber and a media chamber, with a diameter of ≥ 5 cm having an inlet connected to a liquid tank via a 1st valve, an outlet connected to an eluate tank via a 2nd valve, and a fluid purge orifice connected to the outlet via a 3rd valve, a double-acting piston that includes a plate, having an upper face and a lower face, and a rod. The piston is located within the chromatog. column for compressing the stationary phase between the lower face of the plate and the bottom of the chromatog. column. A hydraulic pump provides fluid to the double-acting piston.

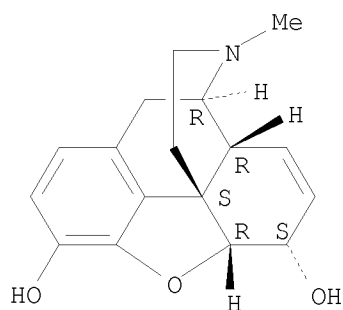
IT 57-27-2P, Morphine, preparation

RL: PUR (Purification or recovery); PREP (Preparation)
(separation and purification of narcotic alkaloids using reversed-phase preparative chromatog.)

RN 57-27-2 CAPLUS

CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-
(5 α ,6 α)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1994:686684 CAPLUS

DOCUMENT NUMBER: 121:286684

ORIGINAL REFERENCE NO.: 121:52227a

TITLE: High-performance liquid chromatography for small-scale studies of drug stability

AUTHOR(S): Hagan, Robert L.

CORPORATE SOURCE: Analytical Research Laboratory, David Grant USAF Medical Center, Travis Air Force Base, CA, 94535-1800, USA

SOURCE: American Journal of Hospital Pharmacy (1994), 51(17), 2162-75

CODEN: AJHPA9; ISSN: 0002-9289

DOCUMENT TYPE: Journal; General Review

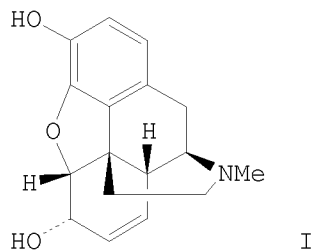
LANGUAGE: English

AB A review with 10 refs. The fundamentals of high-performance liquid chromatog. (HPLC), as applied in small-scale studies of drug stability, are presented. Chromatog. is the separation of a complex mixture into its individual compds. through partitioning between a mobile phase and a stationary phase. A high-performance liquid chromatog. consists of

mobile-phase reservoirs, pumps, a mixer to mix the solvents, a valve into which the sample is injected, a guard column, a column containing the stationary phase, a detector, and a recorder. Once compds. have been separated in the column, they pass into the detector, where an electronic signal corresponding to the amount of compound present is recorded as a peak in a chromatogram. The most common detection method is UV and visible light spectroscopy. Key concepts in HPLC theory are retention time, the time from injection of the sample to detection of a peak; capacity factor, a measure of retention corrected for the elution of an unretained compound; resolution, a measure of how well two peaks are separated; the selectivity of the method; efficiency, or resolving power; and the degree of symmetry of the peaks produced. Most HPLC sepns. are performed in the reverse-phase mode, which involves a non-polar stationary phase and a largely polar mobile phase. Other modes are normal phase, ion exchange, and size exclusion. Before a drug stability study is carried out, an HPLC method must be developed that suits the needs of the proposed experiment. A thorough literature search is essential. Literature procedures serve as useful starting points but may require a great deal of manipulation. After the HPLC separation has been performed, it is necessary to validate the method used. It must be proved that the method is stability indicating, that the chromatog. stds. were properly prepared, that the standard curve is acceptable, and that the method is both precise and accurate. Pharmacists who ensure that reliable, reproducible HPLC methods are used throughout studies of drug stability will obtain sound data that may be of great value in pharmacy practice.

L11 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1983:107 CAPLUS
 DOCUMENT NUMBER: 98:107
 ORIGINAL REFERENCE NO.: 98:15a,18a
 TITLE: Analysis of morphine in serum by high performance liquid chromatography with amperometric detection
 AUTHOR(S): Vandenberghe, H.; MacLeod, S. M.; Chinyanga, H.; Soldin, S. J.
 CORPORATE SOURCE: Dep. Clin. Biochem., Univ. Toronto, Toronto, ON, Can.
 SOURCE: Therapeutic Drug Monitoring (1982), 4(3), 307-14
 CODEN: TDMODV; ISSN: 0163-4356
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB A rapid and sensitive micromethod for morphine (I) [57-27-2] determination in serum or plasma using high performance liquid chromatog. with electrochem. detection is described. The separation of morphine and the internal standard, 5-hydroxyquinoline, from interfering compds. present in

plasma was achieved by paired-ion reverse phase chromatog. using a 70 mM phosphate buffer at pH 5.80. The flow rate was 1 mL/min. Oxidation of morphine and the internal standard was obtained

at a potential of 0.60 V. Only 100 μ L of serum or plasma was required. Anal. recoveries for morphine and 5-hydroxyquinoline were determined as 78% and 63%, resp. The between-day precision of serum samples containing 250, 100, and 25 μ g/L of morphine was 6.5%, 5.2%, and 9.5% resp. The detection limit was 1 μ g/L at a sensitivity of 5 nA/V. Children between the ages of 0 and 5 yr received a bolus of morphine of 11 μ g/kg, followed by an infusion of 2 μ g/kg/min during surgery. The time-concentration curves demonstrated an initial rapid fall in morphine concentration with subsequent attainment of a steady state concentration of approx. 90 μ g/L after 1 h. This concentration would be expected to produce optimal analgesia in conscious patients.

IT 57-27-2, analysis

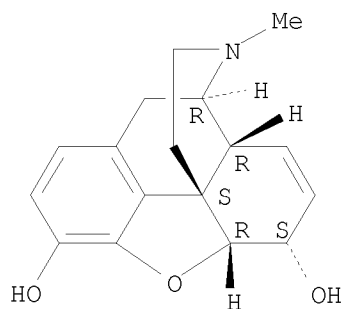
RL: ANT (Analyte); ANST (Analytical study)

(determination of, in blood by high-performance liquid chromatog., pharmacokinetics in children in relation to)

RN 57-27-2 CAPLUS

CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-
(5 α ,6 α)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1981:127428 CAPLUS

DOCUMENT NUMBER: 94:127428

ORIGINAL REFERENCE NO.: 94:20751a,20754a

TITLE: Quantitative determination of opium alkaloids by liquid chromatographic methods

AUTHOR(S): Matantseva, E. F.; Gladyshev, P. P.; Goryaev, M. I.; Bektenova, G. A.

CORPORATE SOURCE: Inst. Khim. Nauk, Alma-Ata, USSR

SOURCE: Khimiya Prirodnykh Soedinenii (1980), (5), 730-1
CODEN: KPSUAR; ISSN: 0023-1150

DOCUMENT TYPE: Journal

LANGUAGE: Russian

AB Ion-exchange and reverse-phase chromatog. is

described for separating phenolic and nonphenolic alkaloids from Papaver somniferum capsules using P-cellulose, Bondapak CX/Corasil, and Bondapak C18/Corasil adsorbents. The eluents for the 3 adsorbents were 0.1N Na phosphate buffer (pH 7.5), 0.1N Ca phosphate buffer with 30% MeCN (pH 4.8), and 0.1N Ca phosphate buffer with 30% MeCN (pH 7.5). The wave length used for the monitoring these alkaloids was 254 nm. The alkaloids separated were morphine [57-27-2], codeine [76-57-3], narcotine

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[128-62-1], thebaine [115-37-7], papaverine [58-74-2], narcotoline [521-40-4], oxydimorphine [125-24-6], narceine [131-28-2], and laudanidine [301-21-3].

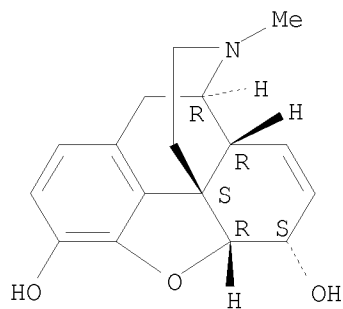
IT 57-27-2, analysis

RL: ANST (Analytical study)
(separation of, from opium alkaloids, by ion-exchange reverse-phase chromatog.)

RN 57-27-2 CAPLUS

CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-
(5 α ,6 α)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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(FILE 'HOME' ENTERED AT 10:04:24 ON 12 JUN 2009)

FILE 'REGISTRY' ENTERED AT 10:04:49 ON 12 JUN 2009

E MORPHINE/CN

L1 1 S E3

FILE 'CAPLUS' ENTERED AT 10:05:20 ON 12 JUN 2009

L2 29660 S L1

L3 1221125 S SEPARATION OR PURIFICATION

L4 956 S L2 AND L3

L5 3586 S REVERSE PHASE CHROMATOGRAPHY OR PREPARATIVE CHROMATOGRAPHY

L6 3 S L4 AND L5

L7 48 S NON-POLAR STATIONARY PHASE

L8 66 S POLAR MOBILE PHASE

L9 1 S L7 AND L8

L10 0 S L2 AND L9

L11 4 S L6 OR L9

=> d l1

YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y

THE ESTIMATED COST FOR THIS REQUEST IS 2.05 U.S. DOLLARS

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN

RN 57-27-2 REGISTRY

ED Entered STN: 16 Nov 1984

CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-

10/501,353

(5 α ,6 α)- (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Morphinan-3,6 α -diol, 7,8-didehydro-4,5 α -epoxy-17-methyl- (8CI)

OTHER NAMES:

CN (-)-Morphine

CN Aguettant

CN DepoDur

CN Dinamorf

CN Dulcontin

CN Duromorph

CN l-Morphine

CN M-Eslon

CN Meconium

CN Morphia

CN Morphin

CN Morphina

CN Morphine

CN Morphinism

CN Morphinum

CN Morpium

CN MS Contin

CN Nepenthe

CN Ospalivina

CN Sevredol

CN Statex SR

FS STEREOSEARCH

DR 863713-90-0, 8053-16-5, 85201-37-2, 47106-99-0

MF C17 H19 N O3

CI COM

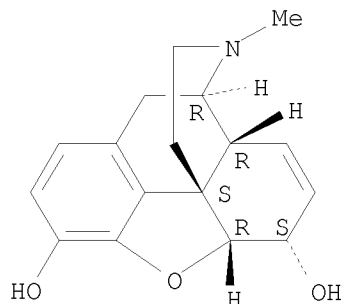
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSPATENTS, IMSPRODUCT, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD, VETU

(*File contains numerically searchable property data)

Other Sources: EINECS**

(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

29614 REFERENCES IN FILE CA (1907 TO DATE)

350 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

29657 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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